

**REMARKS/ARGUMENTS**

Claims 23-24, 26, 28-37 are currently pending in the above-identified application. By this submission, claim 23 has been amended to delete the phrase "no additional cytokine". No new matter has been added by these amendments. Applicants respectfully request reconsideration of the claims currently pending in the application in light of the amendment above and the remarks below.

**Rejections Under 35 U.S.C. § 112**

Claims 23-24, 26, 28-37 stand rejected under 35 U.S.C. §112, first paragraph, the Examiner believing that the specification does not contain a written description of the claimed invention. In particular, the Examiner does not believe that the limitation "no additional cytokine" as recited in independent Claim 23 and dependent claims 24, 26, and 28-37 has clear support in the specification and the claims as originally filed.

Although Applicants disagree with Examiner's reasons for rejection, Claims 23 has been amended to delete the phrase "no additional cytokine" in order to further clarify the subject matter claimed. Claims 23, 24, 26 and 28-37 are believed to be fully supported by the specification as filed and the amendment is not believe the alter the scope of the claims. The Examiner is respectfully requested to reconsider and withdraw the present rejection.

**Rejections Under 35 U.S.C. § 103**

Rejection under 35 U.S.C. §103(a) of claims 23, 24, and 31-36 pertaining to being obvious over Cohen *et al.* (U.S. 5,643,786, of record), in view of Sallusto *et al.* (*J. Exp. Med.* 179:1109-1118, 1994), of record, and Inaba *et al.*, (*J. Exp. Med.* 166:182-194, 1987), of record, remains for reasons already of record in the paper dated June 17, 2004. In particular, the Examiner believes that Cohen *et al.* teach that certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion achieved with calcium ionophore: these cytokines include rhIL-12, rhGM-CSF, rhIL-4 and rhIL-2, and

that each cytokine when given alone is inadequate for optimal upregulation (column 10, lines 54-60). The Examiner goes on to state that "[i]n other words, this passage from Cohen *et al.* clearly teaches that certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion of monocytes, which could be also achieved with calcium ionophore." Further, the Examiner believes that in this passage, Cohen *et al.* do not teach that the monocytes have to be treated first with calcium ionophore before treating with cytokines citing as an example step 8 where Cohen *et al.* teach that in **some instances** (emphasis added) that the combination of cytokines rhIL-12, rhGM-CSF, rhIL-4 and rhIL-2 is added to monocytes that have been exposed to calcium ionophore.

The Examiner further contends that although Cohen *et al.* do not teach the details of how to activate monocytes exposed to prostate cancer cell lysate, this is compensated by Sallusto *et al.* who teach that the specific combination of GM-CSF and IL-4 provide the best conditions for the generation of cells with characteristic phenotypes and functional properties of dendritic cells. Also, the Examiner believes that it would have been obvious to:

- 1) isolate the monocytes as taught by either Cohen *et al.* or Sallusto *et al.*,
- 2) activate these monocytes using the specific combination of GM-CSF and IL-4 which provides the best results, as taught in the detailed method of Sallusto *et al.* as an alternative method to the calcium ionophore method of activating monocytes specific for prostate cancer antigen, taught by Cohen *et al.*, in view of the teaching of Cohen *et al.* that certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion of monocytes, and further in view of successful activation of monocytes by GM-CSF and IL-4, taught by Sallusto *et al.*, and
- 3) expose these monocytes to prostate cell lysate, as taught by Cohen *et al.*, for them to present prostate tumor antigen, for potential use in prostate cancer treatment, as suggested by Cohen *et al.*

The Examiner believes that one would have had a reasonable expectation of success in obtaining an activated dendritic cell population that could present prostate tumor antigen, in view of the teaching of Sallusto *et al.* that exposure of monocytes or blood mononuclear cells to a combination of cytokines, such as GM-CSF and IL-4 would convert them to immature dendritic cells, that could efficiently present soluble antigen to activate specific T cells. Further, the Examiner believes that although Sallusto *et al.* do not teach prostate cancer cell lysate antigen, that is compensated for by Cohen *et al.*, who teach that the activated monocytes could then be exposed to prostate tumor antigen for its presentation, for increasing the immune response to the tumor cells (Cohen *et al.*, Example 2 on column 12).

Previously Applicants have argued that Cohen *et al.* teach away from the invention, because Cohen *et al.* compare various cytokine combinations as being inferior to calcium ionophores, and provide a prophetic example of a treatment method that cannot process and present any soluble antigen, much less a prostate tumor cell lysate. Applicants have also demonstrated that the cells obtained by the method of Cohen *et al.* are mature dendritic cells and are unable to process antigen as would be required for the prophetic example described in Cohen to work. The Examiner has again not found these arguments be to persuasive.

Contrary to Applicant arguments, the Examiner believes that Cohen *et al.* does not teach away from the invention. In particular, the Examiner believes that although, Cohen *et al.* teach that no added other reagents, such as cytokines are as effective as calcium ionophore in upregulate the dendritic cell population, Cohen *et al.* teach that however, certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion achieved with calcium ionophore. The Examiner continues that in other words, although cytokines, when added with calcium ionophore are not as effective as calcium ionophore, a certain combination of cytokines, when by themselves, without calcium ionophore, are successful to amplify or partially substitute for the activation dendritic cells, that could have been achieved with calcium ionophore.

Still further, the Examiner believes that Cohen *et al.* provide the motivation for substituting calcium ionophore with cytokines, with the teaching that a certain combination of cytokines are successful to amplify or partially substitute for the activation dendritic cells, that could have been achieved with calcium ionophore. The Examiner again asserts that concerning Applicant comment that Cohen *et al.* provide a prophetic example of a treatment method that cannot process and present any soluble antigen, much less a prostate tumor cell lysate, it is noted that Applicant argues limitation not in the claims.

Also, the Examiner believes that Inaba *et al.* clearly teach that dendritic cells are a major if not essential accessory cell for the activation of both subpopulations, CD4<sup>+</sup> and CD8<sup>+</sup> (citing figures 1-2 on page 184, and Summary on page 192) and further, that one would have expected that the dendritic cells activated in vitro by the method of Sallusto *et al.* would have the same properties and characteristics as isolated dendritic cells, taught by Inaba *et al.*, because Sallusto *et al.* teach that the specific combination of GM-CSF and IL-4 provide the best conditions for the generation of cells with characteristic phenotypes and functional properties of dendritic cells and are the most efficient in presenting soluble antigen. Additional portions of the results obtained by Inaba *et al.* are cited by the Examiner as demonstrating that it is the properties of activated CD4<sup>+</sup> and CD8<sup>+</sup> cells to be antigen-specific, and to function as killer cells, summarizing that, since it is the properties of dendritic cells to activate CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells, wherein said T cells are antigen-specific, and wherein said antigen could be any antigen, including a tumor antigen, one would have expected that the dendritic cells taught by Cohen *et al.* and Sallusto *et al.* would activate prostate cancer antigen-specific CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells.

Applicants again strongly object to the Examiner's overly broad and unwarranted extrapolations of the teachings of Cohen *et al.*, individually and in any combination with Sallusto *et al.* and/or Inaba *et al.*. Therefore, in order to further expedite prosecution of the pending claims, Applicants provide attached hereto a Declaration by Dr. Alton Boynton, an inventor in the present application, that establishes either conception and reduction to practice in the United States of the subject matter of the rejected claims prior to the effective date of the Cohen reference, January 27, 1995, or conception of the invention prior to January 27, 1995 coupled

with due diligence from prior to January 27, 1995 to a subsequent reduction to practice or to the filing of the parent application on July 31, 1995. Therefore, Cohen *et al.* is not prior art to the present application.

The Boynton Declaration shows that Applicants invention was conceived and reduced to practice prior to January 27, 1995, the filing date of the application that matured into U.S. Patent 5,643,786, or that the invention was conceived of prior to January 27, 1995 coupled with due diligence from prior to January 27, 1995 to a subsequent reduction to practice or to the filing of the parent application on July 31, 1995. (See Boynton Declaration at paragraphs 4 through 12; see also Exhibit A). First, the Boynton Declaration notes that the manuscript entitled "*In vitro* propagated dendritic cells from prostate cancer patients as a component of prostate cancer immunotherapy" co-authored by Benjamin Tjoa, Sheila Erickson, Robert Barren III, Haakon Ragde, Gerald Kenny, Alton Boynton, and Gerald Murphy (herein "the Tjoa *et al.* reference" and attached as Exhibit A to the Boynton Declaration), was submitted to the editors of The Prostate November 5, 1994 and published in The Prostate Volume 27:63-69, August 1995. (copy attached as Exhibit B of the Boynton Declaration). This date was prior to the effective date of Cohen *et al.* Further, a revised version of the manuscript was submitted to the editors of The Prostate and accepted for publication April 2, 1995. The revised manuscript included the same experimental data as the original manuscript and did not substantively alter the scope of the subject matter disclosed.

Exhibit A attached to the Boynton Declaration is a copy of the manuscript as submitted and accepted by the editors of The Prostate. Exhibit B attached to the Boynton Declaration is a copy of the Tjoa *et al.* reference. The Tjoa *et al.* reference and the manuscript describe studies reporting the *in vitro* propagation of dendritic cells from the peripheral blood of prostate cancer patients in GM-CSF and IL-4. (See paragraph 6 of the Boynton Declaration). The cells were cultured for seven days and after this culture period the number of dendritic cells recovered were 20 to 50 fold higher than those isolated directly from peripheral blood and was described as similar to the number of dendritic cells obtained in a comparable study with healthy individuals. The cultured dendritic cells were also shown to be capable of presenting tetanus

toxoid to autologous T cells *in vitro* and T cells from 2 or 4 patients were demonstrated to proliferate when cultured with the patients dendritic cells and a lysate from the human prostate cell line LNCaP. Additional prostate antigens that can be used in the methods were also described in the Tjoa *et al.* reference. (See Boynton Declaration paragraph 6).

The studies described in the Tjoa *et al.* manuscript and reference are the same as those described in the U.S. Patent Application No. 08/509,254, filed July 31, 1995 from which the present application is a continuation-in-part. (See for example, pages 16-24 and Figures 1 through 4 of the '254 application). The same disclosure can be found at, for example, pages 19-27, and Figures 1 through 4, of the present application. These studies clearly demonstrate that the present invention was conceived of and reduced to practice either prior to January 27, 1995 or conception coupled with due diligence from prior to January 27, 1995 to a subsequent reduction to practice or to the filing of the parent application on July 31, 1995.

As shown by the Boynton Declaration, although Sheila Erickson, Robert Barren III, Haakon Rage, and Gerald Kenny are named as a co-author on the Tjoa *et al.* reference (Exhibit B), as they did not participate in the conception of the subject matter disclosed and claimed in the '254 application or the present application, they are not an inventor of the invention as currently claimed. (See Boynton Declaration at paragraphs 8 through 10).

Further, between November 5, 1994 and the filing date of the '254 application additional experiments were diligently carried out in the United States that describe, for example, the isolation of prostate specific membrane antigen (PSMA), T cell proliferative responses and cytotoxic responses induced by dendritic cells presenting PSMA, the use of cryopreserved dendritic cells, and the use of PSMA peptides to stimulate T cells. (See Boynton Declaration paragraph 11) The parent '254 patent application was also prepared, revised and filed during this time period and includes the experiments as, for example, portions of sections 6.1.3, and 6.3, section 7, 8 and 9, and Figures 5 through 9.

Accordingly, one of skill in the art would accept Applicants' possession of the present invention prior to January 27, 1995 or conception coupled with due diligence from prior to January 27, 1995 to a subsequent reduction to practice or to the filing of the parent application on July 31, 1995 as evidenced by Exhibits A and B. (See Boynton Declaration paragraph 12.

In light of the above, Applicants submit that Cohen *et al.* is not prior art with respect to the pending claims. As the primary reference for the present rejection under 35 U.S.C. 103(a) has been removed, the secondary references Sallusto *et al.* and Inaba *et al.* either alone or in combination do not disclose or suggest the present invention. In particular, Sallusto *et al.* do not address tumor cell lysates or other "normal" tumor antigens and does not anticipate their use for therapeutic purposes. As to Inaba *et al.*, Inaba *et al.* teach the use of dendritic cells to stimulate T cells, but T cell activation was only demonstrated for *ex vivo* isolated cells, not dendritic cells that have been derived from *in vitro* cultured monocytes. Furthermore, Inaba *et al.* describe the stimulation of T cells in a mixed lymphocyte reaction and does not describe the uptake or processing of any antigen much less a prostate tumor cell lysate. Also, the T cell activation measured by mixed lymphocyte reaction is a non-specific T cell activation, not an antigen specific T cell activation as required by the present claims. Still further, Inaba *et al.* state at page 192, "[o]f some interest is the role of dendritic cells in the primary response to viral and tumor antigens on other cells. Are antigens on infected or malignant cells presented directly to unprimed CD8<sup>+</sup> T lymphocytes or via a dendritic cell in the host?". Therefore, Inaba *et al.* does not appear to provide any motivation to the skilled artisan to expect that the properties of, for example, Sallusto *et al.* would activate CD4<sup>+</sup> or CD8<sup>+</sup> T cells. Therefore, the present invention as claimed is not obvious over Sallusto *et al.* and/or Inaba *et al.* either individually or in any combination.

Claim 26 remains rejected under the 35 U.S.C. §103 as being obvious over Cohen *et al.*, in view of Sallusto *et al.*, and Inaba *et al.*, and further in view of Lutz *et al.* for reasons already of record in paper of August 20, 2003. The Examiner believes that the claimed dendritic composition is obvious in view of the composition of dendritic cells taught by Cohen *et al.*, Sallusto *et al.*, and Inaba *et al.*, *supra*. Further, the Examiner believes that Lutz *et al.* render the

claimed immortalized dendritic cells obvious, because Lutz *et al.* teach how to make immortalized dendritic cells to overcome the problem of being unable to maintain dendritic cells in vitro for long periods of time.

As above, Cohen *et al.* is not prior art to the presently pending claims. Also as above, Applicants have demonstrated that neither Sallusto *et al.*, alone or in any combination with Inaba *et al.*, teach nor suggest the dendritic cell compositions of the present invention. Therefore, Lutz *et al.* adds nothing to render obvious the immortalized dendritic cells of the invention as either previously or presently claimed.

Claims 28 and 29 remain rejected under 35 U.S.C. § 103 as being obvious over Cohen *et al.*, in view of Sallusto *et al.*, and Inaba *et al.*, and further in view of Taylor *et al.* for reasons already of record in the paper of August 20, 2003. The Examiner continues to believe that the claimed dendritic composition is obvious in view of the composition of dendritic cells taught by Cohen *et al.*, Sallusto *et al.*, and Inaba *et al.*, *supra*. Further, the Examiner believes that Taylor *et al.* render the claimed cryopreserved dendritic cells obvious, because Taylor *et al.* teach how to cryopreserve dendritic cells for use in immunological procedures.

As above, Cohen *et al.* is not prior art to the presently pending claims. Also as above, Applicants have demonstrated that neither Sallusto *et al.*, alone or in any combination with Inaba *et al.*, teach nor suggest the dendritic cell compositions of the present invention. Therefore, Taylor *et al.* adds nothing to render obvious the preserved dendritic cells of the invention as either previously or presently claimed.

Claim 30 remains rejected under 35 U.S.C. § 103 as being obvious over Cohen *et al.*, in view of Sallusto *et al.*, and Inaba *et al.*, and further in view of Taylor *et al.* and Lutz *et al.*, for reasons already of record in the paper of August 20, 2003. The Examiner continues to believe that the claimed composition is obvious in view of the composition of dendritic cells taught by Cohen *et al.*, Sallusto *et al.*, and Inaba *et al.*, *supra*. Further, the Examiner believes the motivation to combine the teaching of Cohen *et al.*, Sallusto *et al.*, and Inaba *et al.*, with Taylor

*et al.* and Lutz *et al.*, is for preserving the dendritic cells taught by Cohen *et al.* and Sallusto *et al.*, for use in immunological procedure, as taught by Taylor *et al.*, and for immortalizing dendritic cells to overcome the problem of being unable to maintain dendritic cells in vitro for long periods of time, as taught by Lutz *et al.*

As above, Cohen *et al.* is not prior art to the presently pending claims. Also as above, Applicants have demonstrated that neither Sallusto *et al.*, alone or in any combination with Inaba *et al.*, teach nor suggest the dendritic cell compositions of the present invention. Therefore, neither Taylor *et al.* or Lutz *et al.* alone or in any combination adds anything to render obvious the immortalized dendritic cells of the invention as either previously or presently claimed. There also is no motivation for one of skill in the art to combine the references.

In view of the above amendments, the Boynton Declaration, and the remarks above, Applicants respectfully request the Examiner to reconsider and withdraw the various rejections of claims 23, 24, 26, and 28-36 under 35 U.S.C. § 103 as being obvious over Cohen *et al.*, in view of Sallusto *et al.* and Inaba *et al.* and further in view of either Taylor *et al.* and/or Lutz *et al.* alone or in combination. In particular, as the Cohen *et al.* reference has been removed as a prior art reference and Applicants have been demonstrated the pending claims to be non-obvious over any remaining reference alone or in any combination, it is further requested that the various rejections of the claims under 35 U.S.C. § 103 be withdrawn.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an

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early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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